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EXAMINER	
POLANSKY, GREGG	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,545	FISCHER, PETER	
	Examiner	Art Unit	
	Gregg Polansky	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's response to the previous office action, canceling Claim 7, modifying Claims 8, 9, and 12, and adding new claims 17-20, filed 7/13/2007, is acknowledged.

2. Claims 8-20 are pending.

3. Claims 8-20 are under consideration.

4. It is noted that although Claim 8 has been amended by the Applicant, the status identifier recites "previously presented".

Specification

5. The abstract of the disclosure is objected to because it is not descriptive of the elected invention. The abstract should be between 50 and 150 words in length and should specifically provide a description of the elected invention.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Instant Claim 8 recites "a method of treating a patient comprising: diagnosing the patient with a non-anticholinergic state of delirium...". There is insufficient written basis for the method of making a diagnosis of non-anticholinergic delirium in the Specification. 35 U.S.C. 132 prohibits introduction of new matter into the disclosure of application; 35 U.S.C. 112, first paragraph, requires that claim language be supported in specification. See *In re Rasmussen* 211 USPQ 323.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The Specification defines non-anticholinergic deliria as "deliria which occur without anticholinergically acting substances being administered beforehand" (*see* page 5, 2nd paragraph). The Specification discloses that the determination of the cause of deliria is "extremely complex and time-consuming" "due to the plurality of possible causes" and that a drug-induced delirium is assumed (*see* page 5, last paragraph, lines 2-8). However, the Specification also discloses that the object of the invention is to

"make available treatment of non-anticholinergic states of delirium, which can be promptly and universally used without the need for extremely complex study of causes" (*see* page 6, "Summary of the Invention", 1st paragraph). Determining if a drug has anticholinergic activity can be difficult. For instance, Rupreht et al. (English translation from Ann. Fr. Anesth. Reanim., Vol. 9, 1990) teach that the mechanism by which gaseous and intravenous anesthetics (not generally considered to be anticholinergic drugs) produce symptoms of a central cholinergic blockade (e.g., delirium) are not completely understood, but the therapeutic effects of treatment with physostigmine indicates that general anesthesia is capable of inhibiting cholinergic transmission (*see* page 7, lines 1-4). Therefore, any drug that causes delirium and is effectively treated by an acetylcholinesterase inhibitor could be said to be an anticholinergic drug, even though its main classification may not be that of an anticholinergic drug.

Therefore, the Applicant fails to disclose how to diagnose a patent with non-anticholinergic deliria so that said patient may be promptly treated by the instant invention.

8. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the Written Description requirement. The claim contains subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 18 recites the limitation "internal disease". However, the Specification does not teach which internal diseases the Applicant contemplates as being capable of causing deliria that are treatable by the instant invention.

Virtually any disease can be considered an internal disease. These would include diseases of the heart, kidney, liver, brain, gastrointestinal and genitourinary systems, cancers, etc., which would further include more specific diseases (e.g., different forms of cancer, renal failure, renal stones, diabetes (insipidus, and mellitus types I and II), etc.).

Without clearly specifying in the Specification which internal diseases the Applicant contemplates as being capable of causing deliria that are treatable by the instant invention, one skilled in the art could not conclude that the inventor, at the time the application was filed, had possession of the claimed invention.

9. Claims 8-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the Enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing

many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treating a patient experiencing delirium that was not caused by anticholinergic drugs, by administering to said patient an effective amount of an acetylcholinesterase inhibitor. Thus, the claims taken together with the specification suggest a treatment of delirium of **any type and cause** (other than anticholinergic drugs) by administering an acetylcholinesterase inhibitor. Additionally, Claim 9 is drawn to a method of treating a patient experiencing delirium **caused by postoperative complications** and was not caused by anticholinergic drugs.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The Merck Manuals Online Medical Library ("Delirium", http://www.merck.com/mmhe/sec06/ch083/ch083b.html#sb083_1) teaches that there are many diverse causes of delirium. The reference teaches that the causes of delirium, as follows (*see* "Causes", pages 1-2 of printed version):

> Development or worsening of almost any disorder can cause delirium. Any person can become delirious when they are extremely ill or are taking drugs that affect brain function. However, delirium can result from less severe conditions in older people and in people whose brain has been affected by a stroke, dementia, or other disorders that cause nerve degeneration. In such people, delirium can result from a relatively minor illness, such as retention of urine or feces; sensory deprivation, such as

that due to being socially isolated or not wearing glasses or hearing aids; or prolonged sleep deprivation. For example, the sensory and sleep deprivation that occurs in intensive care units (ICUs) may contribute to delirium. This disorder is sometimes called ICU psychosis.

Being in the hospital can also contribute to or trigger delirium. About 10 to 20% of older people develop delirium *while* they are in the hospital. Delirium is also very common after surgery, probably because of the stress of surgery, the anesthetics used during surgery, and the analgesics used after surgery.

The most common reversible cause of delirium is drugs. Delirium may result from use of a drug or from withdrawal of a drug that has been taken for a long time. In younger people, ingestion of poisons (such as rubbing alcohol or antifreeze), use of illicit drugs, or acute intoxication with alcohol are common causes of delirium. In older people, prescription drugs are usually the cause. Psychoactive drugs, such as opioids (including morphine and meperidine), sedatives (including benzodiazepines), antipsychotics, and antidepressants, impair brain function by their direct effects on nerve cells. Delirium may result. Drugs with anticholinergic effects, including many over-the-counter (OTC) antihistamines, may cause delirium. Amphetamines, which are stimulants, may also cause delirium. Sudden withdrawal of a sedative (such as a benzodiazepine or barbiturate) that has been taken for a long time frequently results in delirium. Delirium commonly occurs in alcoholics who suddenly stop drinking alcohol and in heroin users who suddenly stop using heroin.

Abnormal blood levels of electrolytes, such as calcium, sodium, or magnesium, can interfere with the metabolic activity of nerve cells and lead to delirium. Abnormal electrolyte levels may result from use of a diuretic, dehydration, or disorders such as kidney failure and widespread cancer. An underactive thyroid gland (hypothyroidism) causes delirium with lethargy; an overactive thyroid gland (hyperthyroidism) causes delirium with hyperactivity.

In younger people, the cause of delirium is usually a condition that directly affects the brain—for example a brain infection, such as meningitis or encephalitis. In older people, the cause is usually drugs or a disorder that affects other parts of the body—for example, an infection that affects the brain indirectly, such as a urinary tract infection, pneumonia, or influenza.

Agents or conditions that have an inhibitory effect on the central anticholinergic system can cause delirium. Cholinergic transmission may be blocked by anticholinergic drugs or reduced by agents or conditions that interfere with the release or turnover of acetylcholine (*see* Rupreht et al., *ibid*, page 2, 1st paragraph). These agents or conditions include drugs that do not possess primary anticholinergic effects but reduce cholinergic activity by reducing synaptic acetylcholine release by action on other neurotransmitters (e.g., reducing excitatory GABA presynaptic stimulation of acetylcholine release, or hypoxia decreasing acetylcholine synthesis). For instance, it has been demonstrated that hypoglycemia, decreases acetylcholine synthesis in the cortex and striatum (*see* Flacker et al., [The Journals of Gerontology, Vol 54A, 1999], page B240, lines 2-4). Rupreht et al. also teach that "most anesthetic agents probably interfere with the central cholinergic transmission, it must be systematically envisioned that a disturbed postanesthetic arousal [e.g., delirium] may be partially or totally due to CAS" (*see* page 7, 17-20). Parikh et al. (Anesth. Analg., Vol 80, 1995) teach of a study that suggests that an increase of serum cortisol from the stress of surgery or anesthesia may be responsible for postoperative confusion (*see* page 1224, middle of second column). The Merck Manual teaches that the "treatment of delirium depends on its cause. For example, doctors treat infections with antibiotics, dehydration with fluids and electrolytes given intravenously, and delirium due to alcohol withdrawal with benzodiazepines..." (*see* "Treatment and Prognosis", pages 4-5).

Since the causes of delirium are numerous, and the determination of the etiology, complex, the outcome of treatment is unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is that of one possessing a medical degree or a Ph.D. in clinical pharmacology.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for treating deliria caused by agents or conditions that diminish central cholinergic activity (e.g., decreased transmission as a result of blocking central cholinergic receptors, inhibiting acetylcholine release, enhancing synaptic acetylcholine metabolism, or effecting presynaptic inhibitory receptors), as demonstrated by a therapeutic effect of an acetylcholinesterase inhibitor (enhancing acetylcholine synaptic concentration).

An example is provided, demonstrating treatment of one individual experiencing lithium induced delirium, through the administration of the acetylcholinesterase inhibitor, rivastigmine.

However, the specification does not provide guidance for treating **all causes of delirium**, including those that do not involve the central cholinergic system (and thus, do not respond to acetylcholinesterase inhibitors).

Also, in light of the Rupreht el. al teaching that most anesthetic agents probably interfere with central cholinergic transmission (*supra*), one skilled in the

art would find it difficult to envisage a postanesthetic, non-anticholinergic state of deliria.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regard to the complexity in diagnosis and multitude of causes of deliria and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 103

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 8-10, 13, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupreht et al. (English translation from Ann. Fr. Anesth. Reanim., Vol. 9, 1990).

Claim 8 is drawn to the method of diagnosing and treating a non-anticholinergic drug induced state of delirium in a patient in need thereof, through the use of acetylcholinesterase inhibitors. Claims 9, 10, 13, and 18 are drawn to the method of treating non-anticholinergic drug induced delirium, which is a postoperative delirium or, caused by an internal disease or a hypoglycemic process, through the use of acetylcholinesterase inhibitors.

Rupreht et al. teach the central anticholinergic syndrome (CAS), which includes confusion or delirium occurring during the postoperative period, and caused by medication (e.g., atropine, opioids, halothane, benzodiazepine, anesthetics) and conditions such as, *inter alia*, hypoxia and hypoglycemia (*see* Abstract). Rupreht further teaches that CAS occurs when central cholinergic sites are occupied by specific drugs and also as a result of an insufficient release of acetylcholine (as can be caused by non-anticholinergic drugs; see translation, page 2, 1st paragraph), and can be effectively treated by acetylcholinesterase inhibitors, including, physostigmine, galantamine, tacrine (*see* paragraph spanning pages 7-8). The reference also teaches "molecules free of primary anticholinergic effects may also indirectly reduce central cholinergic activity by modulating the action of other transmitters such as gamma-aminobutyric acid (GABA) intervening in cholinergic activity" (*see* page 2, 1st paragraph). Rupreht et al. teach that the mechanism by which gaseous and intravenous anesthetics produce symptoms of a central cholinergic blockade (e.g., delirium) are not completely understood, but the therapeutic effects of treatment with physostigmine indicate that general anesthesia is capable of inhibiting cholinergic transmission (*see* page 7, lines 1-4).

One of ordinary skill in the art would have concluded that any drug (regardless of its classification as an anticholinergic drug or a "non-anticholinergic drug") or medical condition that causes delirium and is effectively treated by an acetylcholinesterase inhibitor has a central anticholinergic mechanism of causing deliria. Therefore, the acetylcholinesterase inhibitors of the instant invention are treating deliria by the same

mechanism as acetylcholinesterase inhibitors used to treat deliria as taught by Rupreht et al.

Even though Rupreht et al. does not mentioned hypoglycemic coma or resuscitation as the causative factor for delirium (as recited by instant Claims 11 and 12), it would have been obvious to one of ordinary skill in the art at the time of invention to extend Rupreht et al's teaching of acetylcholinesterase inhibitor administration for treating delirium or confusion caused by hypoglycemia, hypoxia and neurological damage resulting from surgery, to delirium caused by hypoglycemic coma and resuscitation. One would have motivated to do so, with a reasonable expectation of success, because Rupreht's teaching (i.e., acetylcholinesterase inhibitor treatment) includes hypoglycemia which encompasses hypoglycemic coma and neurological damages or hypoxia where it is well known in the art that improper resuscitation often causes neurological damages or hypoxia, absent evidence to the contrary.

12. Claims 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Enz (US 5,602,176) in view of Flacker et al (The Journals of Gerontology, Vol 54A, 1999), Parikh et al (Anesth. Analg., Vol 80, 1995), Rupreht et al. (English translation from Ann. Fr. Anesth. Reanim., Vol. 9, 1990) and Pestronk et al. (Brain Research, Vol 412(2), 1987).

Enz teaches a method of treating acute confusion disorders using a pharmaceutical composition comprising a therapeutically effective amount of (s)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl carbamate (rivastigmine: chemical name, used hereafter);see column 5, lines 1-3. Enz also teaches that rivastigmine is

acetylcholinesterase inhibitor; see column 1. The reference also noted that the term "delirium" is a synonym of "acute confusion disorder" as admitted in instant application; see instant specification at page 4, second paragraph (lines 30-32).

However Enz is silent about the etiologies (causative factors) of acute confusion disorder (delirium).

Flacker et al. and Rupreht et al. teach a central cholinergic etiology for delirium (*see* Rupreht et al., Abstract and Flacker et al. page B239, column 2, last paragraph). Parikh et al. teach of a central cholinergic mechanism of postoperative delirium (*see* page 1224, subparagraph 'Pathophysiology'). Furthermore, all teach hypoxia, hypoglycemia, and other "non-anticholinergic" effects on central cholinergic activity and production of delirium. Parikh et al. also teach of delirium caused by fluid and electrolyte imbalance, endocrinopathies like diabetic ketoacidosis, or nonketotic hyperglycemic diabetes, hyper- or hypothyroidism, and hepatic, renal, or pulmonary insufficiency ("internal disease") (e.g., page 1226, column 1, lines 10-25).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select cholinergic CNS effectors (i.e. acetylcholinesterase inhibitors (e.g., rivastigmine)) suggested by Enz, to treat delirium (acute confusion disorder), because both Flacker et al. and Rupreht et al. teach a correlation between decreased central cholinergic activity and delirium, and that the decreased central cholinergic activity could be caused by anticholinergic drugs as well as other factors, such as substance poisoning (equivalent term with intoxication), non-anticholinergic drugs , endogenous anticholinergic substances, hypoglycemia, hypoxia, and metabolic disorders.

13. Claim 16 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janowsky et al. (Psychopharmacology, Vol 63, 1979), and Pestronk et al. (Brain Research, Vol 412(2), 1987), in view of Flacker et al. (The Journals of Gerontology, Vol 54A, 1999), Parikh et al. (Anesth. Analg., Vol 80, 1995), and Rupreht et al. (English translation from Ann. Fr. Anesth. Reanim., Vol. 9, 1990).

Janowsky et al. (*see* Abstract) demonstrate that lithium antagonizes central cholinergic activity.

Pestronk et al (see Abstract), through their examination of acetylcholine metabolism in skeletal muscle, postulate that the mechanism of action of lithium is through modifying the number of acetylcholine receptors (i.e., reduction of the number of acetylcholine receptors).

Flacker et al., Parikh et al, and Rupreht et al. teach an anticholinergic mechanism for deliria and its effective treatment with cholinesterase inhibitors (*supra*).

It would have been obvious to one skilled in the art that delirium caused by lithium intoxication might be through a lithium-induced decrease in central cholinergic activity. One would have been motivated to combine these teachings of a lithium-induced decrease in central cholinergic activity with the teachings of a central cholinergic mechanism in deliria and its effective treatment with acetylcholinesterase inhibitors, to seek a treatment for lithium-induced deliria.

14. Claim 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 5,602,176), in view of Rupreht et al. (English translation from Ann. Fr. Anesth. Reanim., Vol. 9, 1990).

Fisher et al. (Column 5, Lines 39-59) teach the use of a central muscarinic (acetylcholine) agonist in the treatment of conditions which may be caused by central cholinergic hypofunction. They go on to teach that these conditions include acute confusion and alcohol withdrawal ("non-anticholinergic substance withdrawal").

Rupreht et al. teach the role of the central cholinergic system in delirium and of the use of acetylcholinesterase inhibitors in the treatment thereof. Since acetylcholinesterase inhibitors act by increasing the amount of acetylcholine in the cholinergic CNS (and thus increase cholinergic activity), and a cholinergic agonist also results in increased activity of cholinergic neurons, it would have been obvious to one of ordinary skill in the art to combine these teachings.

One would have been motivated to treat non-anticholinergic deliria by administering effectors of the cholinergic CNS, with reasonable expectation of success, because deactivation of the cholinergic nervous system is the biological mechanism for inducing delirium, wherein cholinergic CNS effectors (e.g. acetylcholinesterase inhibitors or acetylcholinergic receptor agonists) effectively and directly activates the cholinergic nervous system and improves the deliria (acute confusion disorder) as suggested by each cited reference.

One would have been motivated to combine these references because they are drawn to same technical fields, use the same or similar ingredients, share common utilities, and are pertinent to the problem with which applicant is concerned. MPEP 2141.01(a).

Response to Arguments

15. Applicant's arguments, with respect to the previous rejections of claims 7-10 and 13 under 35 U.S.C. §102, have been fully considered and are persuasive. Therefore, the rejection has been withdrawn.

16. Applicant's arguments (*see* page 5), with respect to the rejections of claims 11 and 12, which depend from Claim 8, under 35 U.S.C. §103(a), have been fully considered but they are not persuasive.

Applicant states that independent Claim 8 has been amended to better define the subject matter that he regards as the invention. The claim has been modified to include the limitation of diagnosing a patient with non-anticholinergic delirium. However, the Specification does not support this new limitation. The Applicant alleges support for the modification by citing several examples in the Specification. However, the examples do not disclose a method of diagnosing non-anticholinergic deliria. Also, disclosure by example does not teach the full scope of the claimed invention.

Applicant argues that Rupreht only deals with postoperative effects of anticholinergic drugs. However, Rupreht teaches "molecules free of primary anticholinergic effects may also indirectly reduce central cholinergic activity by modulating the action of other transmitters such as gamma-aminobutyric acid (GABA) intervening in cholinergic activity" and that deliria can be cause by, *inter alia*, hypoxia and hypoglycemia (*supra*). Applicant notes that the Examiner listed hypoxia and hypoglycemia as non-anticholinergic medications. The Examiner thanks the Applicant

for pointing this out; they should have been listed under medical conditions which can cause deliria, as is stated in the present Office Action (*supra*).

Applicant argues that Rupreht does not teach or suggest diagnosing a patient with a non-anticholinergic state of delirium. In the present claim rejections, it is stated that one of ordinary skill in the art would conclude that any drug (regardless of its classification as an anticholinergic drug or a "non-anticholinergic drug") or medical condition that causes delirium and is effectively treated by an acetylcholinesterase inhibitor that has a central anticholinergic mechanism of causing deliria. Therefore, the acetylcholinesterase inhibitors of the instant invention are treating deliria by the same mechanism as acetylcholinesterase inhibitors used to treat deliria as taught by Rupreht et al. (*see* rejection explanation under 35 U.S.C. 103, *supra*).

Note: The above response also applies to all of Applicant's arguments since Applicant repeats the above traversal for all claims.

17. Applicant's arguments, see page 5-6, with respect to the rejections of claims 7-14, under 35 U.S.C. §103(a), have been fully considered but they are not persuasive.

Applicant argues that Enz does not teach or suggest diagnosing a patient with a non-anticholinergic state of delirium and that the secondary references also do not teach it.

See Examiner's response to Applicant's traversal of Claim 11 and 12, *supra*.

18. Applicant's arguments, see page 6-8, with respect to the rejections of claim 16, under 35 U.S.C. §103(a), have been fully considered but they are not persuasive.

Applicant argues that "the work of Pestronk is based on muscle acetylcholine receptors, which substantially differ from central acetylcholine receptors in terms of subunit composition and with respect to their response to specific antagonists". However, Applicant provides no support for this assertion.

Applicant argues that Janowsky cites Samples, who found that chronic lithium treatment actually increases the effects of physostigmine. Janowsky adequately explains the discrepancies in their complete discussion on pages 149-150. Their teachings, despite any seemingly conflicting data, would certainly provide adequate motivation to one of ordinary skill in the art to try an acetylcholinesterase inhibitor to treat lithium intoxication. Applicant's assertion that Janowsky nor Pestronk would have suggested to one of skill in the art that a lithium-induced delirium or any other delirium caused by non-anticholinergic intoxication could be treated with a cholinesterase inhibitor is not well taken. Applicant provides lithium-induced delirium as an example of non-anticholinergic intoxication. The Examiner's position is set forth on page 5, lines 4-7.

19. Applicant's arguments, see page 8-9, with respect to the rejections of Claim 15, under 35 U.S.C. §103, have been fully considered but they are not persuasive.

Applicant argues that one of skill in the art would not be motivated to combine the references of Fisher and Rupreht. The Examiner disagrees and refers the Applicant to the present rejection of Claim 15.

Conclusion

20. Claims 8-20 are rejected.

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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